Review of Human Health Risk Assessment

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General: I perceived my main task to be the review of the development and presentation of the risk characterization document itself, especially with respect to the potential human health risks posed by perchlorate. In contrast to other risk characterization documents that I have read, this document is unusual. It really is a work in progress as much as a completed characterization of health and ecological risks posed by perchlorate. Several studies are only partially reported (for instance, the immunotoxicity evaluations) and the development of a more integrated evaluation of the multiple toxic endpoints based on mode-of-action of perchlorate as an inhibitor of iodine uptake by the thyroid is outlined, but only partially implemented. I was also a bit bewildered by the amount of data evaluation/BMD calculations conducted on the various data sets given the final position that the thyroid changes in the post-natal day 5 (PND5) pups would serve as the response for estimating a provisional RfD.

I am greatly in favor of the mode of action based approach for assessing significance of hormonal changes and thyroid histopathology as a sentinel precursor for all relevant responses to perchlorate. I would personally commend the EPA staff for embarking on an integrated analysis of the larger body of data. This approach represents a move in the direction of harmonization of non-cancer and cancer risk assessment paradigms and permits better (i.e., more rational) use of available biological and toxicological data. The presentation of the benchmark dose calculations points out the difficulties faced in fitting various models to the observed response data. Which model form should be applied and how confident are you that you have selected an appropriate mode to represent the data? This section was the most difficult one to follow. Unfortunately, a more comprehensive biological model for assessing curve shapes and assessing the significance of alterations in hormone concentrations has not yet been completely fleshed out, although the data for such an enterprise are apparently available or being collected. (I very much look forward to the presentation on these topics at the stakeholder's meeting as promised on page 6-49.)

Specific Queries from Charge:

II. A. 1. Toxicology Review Document: Key aspects of studies. The presentation and rational for the immunotoxicology studies was not well presented and the labeling of studies by letter designation here was uninformative. Do any of these studies help in considering the importance of the human experience where altered hematology was observed in patients treated with perchlorate? The document states on 3-6 that these effects were apparently due to an immunological response.

II.A. 2. Strengths and Weaknesses of Analyses: The document conveys the results of the various studies in tabular form for the thyroid hormone, TSH, and thyroid effects. These tables present a

large amount of material in a more readily comprehensible fashion. A tabulation of effect levels for specific toxicity in tissues other than the thyroid would also be useful. The presentation of the associations between T3, T4, TSH, and pathological changes is important for confirming a link between the several steps – inhibition of I2 uptake, impaired synthesis/release of T3 and T4, feedback increase of TSH, and overt histological alterations. This section should have an easily followed preamble letting the reader know exactly what is being done and why?

II. A.3. Statistical analyses: I am not the person to respond to questions about adequacy of statistical analyses. In general, I would have preferred that the specifics of the statistical analyses were provided in an appendix with the results and implications emphasized in the text itself.

III.A.4. Missing citations: I am not expert in perchlorate toxicity. There have been models of thyroid function developed previously. These may be helpful in developing the feedback models for assessing 'thyroid hormone economy', although I didn't much care for the word economy here.

II.C.1. Are there sections that could be improved? Probably a good number of the sections can be improved. However, the issue is partially one of organization and emphasis. The document has a conventional RfD assessment portion, i.e., critical study and application of uncertainty factors. It also contains a nascent structure in which mode of action is used to categorize effects and provide a larger structure for interpretation of studies. Some data are interpreted in terms of adequacy of a particular study to assess a NOAEL and others to assess if the precursor effects are consistent with the hypothesis related to precursor thyroid effects. The manner in which these different points are made and emphasized probably deserves more attention. This comment is not so much a criticism as point of emphasis. This presentation mode of action is relatively new for a non-cancer assessment. The authors need to think about how this emphasis might lead to reorganization of the presentation of materials. A possibility in this document is to add material to the Executive Summary that lets the reader know what is coming.

II.C.2. Is the present document useful/should changes be made? Well, of course, its useful in capturing the present state-of-knowledge and pointing out how it should be used. First, most issues about 'other endpoints' have been resolved by the toxicity tests. Unfortunately, many of the studies have not yet been adequately prepared and evaluated for use. Will they be published and undergo peer-review separate from this evaluation? One would hope so. The data supporting a precursor relationship to thyroid dysfunction is well organized, although this hypothesis is not implemented in a way to have much quantitative impact. If a quantitative implementation is planned, it would be useful for a panel to ask the questions of what form the approach will take and will the appropriate kinetic and pharmacodynamic data be available to provide confidence in using a more quantitative approach to guide the risk assessment. In its present form, there is clear documentation about the manner in which the provisional assessment is conducted, but the confidence that the approach will change the assessment low until these studies are all more thoroughly documented and reported.

III.A.1. Are individual NOAELs and LOAELs appropriate given the totality of the data? There are two points here. One is how the mode of action should influence the consideration of the

entire data set; the second is the estimation of the endpoints most sensitive to disruption of thyroid hormone homeostasis. It probably is appropriate and necessary to establish the most sensitive endpoint; however, depending on mode of action, the most sensitive endpoint in a rodent model may not turn out to be the most sensitive endpoint expected in humans. The mode of action and evaluation of the totality of the data base should be especially helpful in the selection of appropriate uncertainty factors after a critical study or several critical studies are identified, along with their NOAEL or LOAEL. A quantitative model may actually render some of the uncertainty factors moot.

III.A. 2. See above III.A.1. As noted it maybe important to select several critical studies. But the critical study is dependent on presumed mode of action and specific characterization of animal human differences in the mode of action.

III. A.3. Should the PND5 results be used as a minimal LOAEL? This position seems sound given the present state of relevant information. One question to ask is the consequences of the observed changes? Do they lead to adverse outcomes in these rats as the mature; are they a compensatory effect related to a temporary impairment in iodide incorporation that will be quickly rectified during nursing and weaning? These questions may require other assessments in the adult rats for altered behavior, etc. Also, are the effects expected in humans? Are there situations that make humans more sensitive at some point in life or less sensitive than the rat?

III.A.4. Is a UCF(a) of 3.0 appropriate? Given (1) the care taken to show the correlation of the various endpoints for thyroid effects, (2) the lack of finding suggesting other modes of action for perchlorate, and (3) the differences in human and rat plasma reserves of thyroid hormones, the factor of 3.0 seems appropriate. Further work on the kinetics of perchlorate in different species and the kinetics of inhibition of the iodide transport mechanisms by perchlorate in rat and human thyroid tissues will be useful in confirming the assumptions above.

III.A.5. Three other corrections were made: each with a value of 3.0. They are for minimal LOAEL versus LOAEL/intrahuman variability, data base deficiencies, and intrahuman variation (sensitive populations). These numbers all together provide a composite correction of 300. Is this sufficient given the data? Probably, because of the knowledge of the mode of action, the knowledge that rats are more sensitive than humans, and the evaluation of effects in the post natal rats. Are these numbers correctly parsed between the individual factors? That is a more difficult call. The data base and minimal LOAEL factors are accessible to experiment, as is the term for interspecies extrapolation above. In general, I become more concerned in reducing the sensitive subpopulation factor from 10, unless specific factors can be cited in support of the change.

III.A.6. Is this really a harmonized assessment? Unequivocally, yes. However, as noted below in this section, the cancer and non-cancer assessments have some differences that still have to be reconciled to use a single approach to derive quantitative numbers for the exposure guidelines. Mode of action has been more frequently (although still very infrequently) applied to cancer risk assessments. In the new US EPA carcinogen guidelines there is provision to discuss mode of

action and to evaluate the possibility that common modes of action could underlie both cancer and non-cancer endpoints. Nasal toxicity with vinyl acetate is an example.

In the present case, the cancer assessment for compounds disrupting thyroid hormone homeostasis have to be extended to consider a much broader set of endpoints than simply carcinogenesis. With the emphasis on MOE approaches for carcinogens with non-linear modes of carcinogenic action, it is likely that certain non-cancer endpoints will become the limiting or critical effects, not the cancer. This is likely true with perchlorate. The alterations in thyroid hormone function **in adults** would probably be used as an obligatory precursor step in a cancer risk assessment. (In adults, since the outcome is related to lifetime exposures, not just the fetal exposure period.) Actually, it would be of interest to calculate a BMD for thyroid disruption in adult rats and follow a non-linear cancer risk assessment paradigm. This exercise would provide a check on the consistency of conclusions reached for cancer and the limiting non-cancer toxicity. As you know, a problem with harmonizing cancer and non-cancer risk assessments is the requirement that the non-cancer assessment decide on values of the uncertainty factors, while the non-linear cancer assessment estimates a margin of exposure (MOE) by comparing a dose-adjusted BMD with presumed human exposure levels. The cancer assessments beg the question of how large does the calculated MOE have to be for the risk assessor to be comfortable. Somehow the comprehensive assessment has to reconcile these two disparate endgames – uncertainty factors versus MOEs. However, I still consider that this document has come closer to achieving a harmonized human health risk assessment than has been done for any other compound here in the USA.

Further Testing:

IV.A.1. With the exception of the immunotoxicology, the test appeared to follow standard protocols accepted by the toxicology community and by EPA. The immunotoxicology requirements and the interpretation of these tests are both still evolving. Nonetheless, I was unsure of the reasons for selecting particular immunotoxicology tests. I cannot specify other test, although it would be wise to conduct standard tests such as the sheep red blood cell test to compare results to other materials. In general, I was surprised that the design criteria used for most of the studies didn't include a review of expected non-cancer endpoints for other iodide uptake inhibitors and considerations of modifying protocols based on that knowledge. (This may well have been a consideration; it's just not apparent from the materials I reviewed.)

IV.A.2. Other tests. My major concern would be with respect to developmental delays or permanent impairment in adult animals following fetal exposures. Have these potential endpoints been adequately examined to rule out higher sensitivity of the fetus to transient periods of hypothyroidism?

IV.A.3. Value added by development of a PBPK model for iodide uptake inhibition, thyroid hormone depletion, hypothyroidism, and compensation. Qualitatively, the mode of action assists in establishing non-linear approaches for cancer risk assessment and in supporting choices for uncertainty values. However, the analysis of dose response curves still rely on external exposure concentrations and on curve fitting to forms that are not concordant with specific biological

processes. That's one of the reasons that someone like this reviewer remains bewildered by the BMD portion of the document.

The development of a PBPK model begins to permit a more quantitative approach to deriving uncertainty factors, to 'fitting' biological models with clearly defined parameters to data, and to inferring the impact of differences between humans and rodents for the risk assessments. What should this 'model' look like? It is important to begin design of the biologically based risk model as soon as a hypothesis is elaborated. In other words, it should be well along the development trail. What is the measure of response or adversity that will be the basis for regulation? Is it some proportionate change in circulating T4/T3, an alteration in TSH, or a characteristic alteration in the cellular structure of the thyroid tissue? This is the most important decision since it forms the objective function against which model performance is to be judged and the output that will organize the assessment. The material presented does not provide adequate basis for commenting on any current model structure, although the methods for the PK, iodide uptake, and thyroid homeostasis models are fairly conventional and efforts in linking these individual elements have been previously reported.

There is inadequate documentation of the data that would be collected for the quantitative model and how it would be used. However, the development of such a quantitative model represents the primary tool needed to move from qualitative application of the broader array of mode of action data to its quantitative impact on risk assessments. The goal is similar to the so-called biologically based dose response models described in the cancer risk assessment guidelines. These models influence analysis in the range of observation and enlighten the extrapolation between species and from high to low doses.

Some specific comments:

1. I found the analogies to parking brakes and hillside parking uninformative. (see, page 2-8). They just don't seem to be necessary for this document. Simply stated perchlorate is stable in biological matrices.

2. page 3-13. One of the potassium chlorates, third line up from the bottom, has the potassium as the labeled isotope vice the chlorine.

3. page 3-14: Perchlorate reduced the thyroid blood ratio of what? Iodide, I presume, although the sentence could be read to indicate perchlorate.

4. Page 3-15: Is it true that the concentration of perchlorate in the thyroid was inversely related to dose, or is the concentration expressed as percent of administered dose related inversely to dose. The former seems hard to reconcile to the behavior of dose-dependent systems.

5. Page 5-18: biological significance is .....suspect. Do you mean .....is uncertain?

6. Page 5-41: The discussion of hints of U-shaped dose response curves probably deserves mention later in the document when discussing limiting toxicity for different endpoints. Is it

real? If it were used as an effect level, does it change the perception of which study gives the lowest adverse effect level? Should anything be done to pursue this observation? I suggest putting this data into the document as a Table with average cycle duration versus dose clearly displayed.

7. Page 5-54. Immunotoxicity – is there any data on immune function in hypothyroid individuals from which hypotheses could be generated about the endpoints that might be most worthwhile to pursue.

8. Page 6-41: exquisite or equisite. I wasn't sure what you meant here. (But I was still reading carefully).

Summary: This document develops both a mode of action based approach to assessing risks of perchlorate. A provisional standard could be set today, but should be refined by new data being collected in response to an earlier review meeting about perchlorate contamination in drinking water. The new data will likely cause re-evaluation soon, if only with respect to ideas of adequacy of data base uncertainty factor. The clearer articulation of a strategy for using mode of action and pharmacokinetic/ thyroid homeostasis data quantitatively would be a useful addition, to the document either in the text or as an Appendix. The harmonization of cancer and non-cancer assessments is appropriate, although not all the issues in the use of the data for conducting a cancer MOE are articulated here. While some reorganization of the document would be helpful for clarity, the assessment collates a large body of information, points the direction for a comprehensive assessment based on mode of action, and provides interim guidance while the data are collected, analyzed, and published.